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10/681,788	10/08/2003	Habib Zaghouani	3718027.00005	6701
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K&L Gates LLP			EWOLDT, GERALD R	
P.O. Box 1135				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/681,788	Applicant(s) ZAGHOUANI ET AL.
	Examiner G. R. Ewoldt, Ph.D.	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 September 2010.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-5,7-13 and 15-30 is/are pending in the application.
 4a) Of the above claim(s) 8-12,20 and 21 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-5,7,13,15-19 and 22-30 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

1. Applicant's remarks filed 9/15/10 are acknowledged.
2. Claims 8-12, 20, 21, and 25 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 7, 13, 15-19, 22-24, and 26-30 are under examination.

3. Upon reconsideration the previous rejection under 35 U.S.C. 103(a) has been withdrawn. Additionally, as Claim 26 depends from Claim 13 which depends from Claim 1, the claim comprises all of Claim 1's limitations, i.e., that the Ig construct of the claim comprises the GAD65 fragment of SEQ ID NO:4. Accordingly, part B) of the previous rejection under the first paragraph of 35 U.S.C. 112 for lack of adequate written description has been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for preventing or delaying the onset of type I diabetes (IDDM) in humans.

As set forth previously, While the mechanism of action for the method of instant claims is not disclosed, it appears to require inducing tolerance to a GAD peptide. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA)

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provided successful results in rodent models (EAE and collagen induced arthritis, respectively). See also Leslie (2010) paraphrasing an interview with Dr. Mark Davis wherein Dr. Davis states that in the case of the administration of MBP for tolerance induction to MBP for the treatment of MS, while the method worked in mice, it actually made MS worse in some humans.

More specifically regarding the treatment of diabetes, see Pozzilli et al. (2000) wherein the authors demonstrate that, while the induction of tolerance to orally administered insulin for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the reasons for the trial's failure. The authors did note one complicating factor that has been reported several times, and will have to be considered in all future work, a large placebo effect wherein both the treated and control subjects showed similar temporary improvement. Three years later Skyler et al. (2005) reported another failure in one of the largest placebo-controlled tolerance trials ever performed in humans (the administration of insulin for the prevention of type 1 diabetes).

As set forth above, the references demonstrate that peptides that work to induce immune tolerance in *in vivo* small animal disease models cannot be routinely expected to work in humans, i.e., they are unpredictable and requiring of undue experimentation.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

"Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn",

emphasis added.

WO 02/053092 teaches that the oral administration of antigens (a route of administration encompassed by the claimed method) for the induction of tolerance presents numerous additional "obstacles", including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that:

"oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation,"

In another attempt to explain these repeated failures Goodnow (2001) states:

"Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles,"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in

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humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

More recently, Kraus and Mayer (2005) looked at tolerance induction in inflammatory bowel disease (IBD). They reported the ease with which tolerance is induced in in-bred experimental mice and contrasted that with the difficulty in inducing tolerance in humans. Speculating on the reasons for the difference the authors considered a lack of dosing optimization but went on to report that the mechanisms of tolerance induction in humans and mice appear to be fundamentally different. Most importantly, Kraus and Mayer report a genetic component wherein many IBD patients and their family members appear to be incapable of becoming tolerant to oral antigens because they lack the ability to generate the required T regulatory cells. If confirmed, this would mean that no tolerance induction regime could work in these patients.

Even more recent work has attempted to duplicate favorable results established in in-bred animal models in a more complex mouse model more realistic to the out-bred human population. See, for example, Bell et al. (2008). The authors employed F₁ hybrid mice (a cross between two in-bred strains) wherein they asked if toleragens that worked in the parent strains would induce tolerance in the crossed F₁ hybrid mice. Unfortunately the results showed that in one instance not only was tolerance not induced, but disease was actually exacerbated. Thus, the work serves as a clear demonstration that the induction of immune tolerance is far from predictable in anything other than carefully chosen in-bred experimental mouse strains.

Also note that Applicant has referred to the NOD mouse as the "gold standard" for diabetes research. Others, however, refer to the NOD mouse as the "workhorse" for diabetes research pointing out the model's limitations. See, for example von Herrath and Nepom (2009). And note that not even all NOD mouse strains are diabetes susceptible, e.g., NOD H-2^k and NOD D98 do not develop the disease. Also note that it is well-known that tolerance to GAD is **not** effective for the treatment of diabetes in another well established diabetes model, the BB rat. Even more recently many scientists have begun to question the value of mouse data altogether. As pointed out by Mark Davis in a recent interview, mice make a "lousy model" for the human immune system. He refers to mice as a short-lived rodent who's immune system has adapted for scurrying around with its nose in the dirt (Leslie, 2010). Also very recently van der Worp et al. (2010) question the value of using animal data to predict the effectiveness of treatment strategies in human trials. As an example, the authors teach that of about 500 effective treatment strategies for stroke in experimental mice, just 2 have proven effective in humans. The authors cite numerous possible reasons for the failed translation of results, including insufficient statistical power, inadequate animal data, overoptimistic conclusions, flawed studies, and the use of animal models that do not reflect real disease in humans. Finally the reference teaches that neutral and negative animal studies may remain unpublished leading to possibly false impressions of efficacy.

A review of the instant specification shows just a single long example wherein a T cell response to a single insulin B chain peptide (amino acids 9-23) is inhibited in the experimental NOD mouse model of IDDM. First note that the instant claims are drawn to the use of GAD, not insulin, for the suspending, preventing or delaying the onset of IDDM. Thus, the specification offers no data in support of the claimed method. Interestingly, the specification discloses, that even regarding the use of an insulin peptide for the suspending, preventing or delaying the onset of IDDM, *the method of the instant claims cannot function as claimed*, emphasis added. For example, at page 28 of the specification, it is

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disclosed that, "Soluble Ig-INS β displayed dose dependent delay of diabetes when given at either stage [pre or post IAA conversion]. However, aggregated Ig-INS β , which induced IL-10 and TGF β -producing T cells, thus involving sustained endogenous IL-10, was protective against diabetes when given before development of insulitis but had no effect in predisposed mice positive for IAA", emphasis added. Further, Examples 7 and 9 teach that neither soluble nor aggregated Ig-INS β can actually prevent IDDM, but rather can only delay onset under specific conditions.

Additionally, Applicant's subsequent work demonstrates that the method of the instant claims would not be expected to function as claimed. See for example Legge et al. (1998). Therein the authors teach that APLs function as, "T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP-1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient. Given that no experiments have been performed employing GAD peptides and derivatives thereof, it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it.

A set forth in *Rasmussen v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

"As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data regarding the treatment or prevention of IDDM employing GAD peptides, and the unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 9/15/10, have been fully considered but are not found persuasive. Applicant cites MPEP 2164.05(a) alleging that post-filing date references cannot be used in an enablement rejection. Applicant then rejects all post-filing references and fails to consider their teachings.

Interestingly, Applicant cites the 8th paragraph of MPEP 2164.05(a) which cites *In re Hogan*. The next sentence in the paragraph states:

"If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the

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application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms."

To concede Applicant's logic would be to concede that the invention functioned as claimed on 4/09/02, but at some not yet determined point after that time, depending on which post-filing references were determined sufficient to support the rejection, the invention stopped functioning and became non-enabled. It remains the Examiner's position that the use of post-filing references in this case is proper.

Applicant continues by arguing against the three references that Applicant finds worthy individually.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As set forth in the rejection, the ten references combined render the claimed invention non-enabled.

Applicant briefly summarizes the disclosure and cites a previous declaration under 1.132 of the Inventor.

The Inventor's declaration was addressed in previous actions and will not be addressed again here.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be

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commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '070 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '084 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant defers a response regarding the remaining rejections until the finding of allowable claims.

9. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter written description rejection.

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As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising the administration of an immunoglobulin construct comprising a protein [fragment] (added 11/12/10) represented by SEQ ID NO:4 (Claims 1 and 13).

Applicant cites pages 13, 21, 45, and 26 in support of the claimed method.

A review of the specification reveals that the peptide of SEQ ID NO:4 is found at page 46 of the specification. The specification, however, does not teach the peptides as part of an immunoglobulin construct. Further, the specification does not teach a peptide consisting of amino acid residues 206-220 of any GAD65, e.g., mouse GAD65, rat GAD65, horse GAD65, etc.

Applicant's arguments, filed 9/15/10, have been fully considered but are not found persuasive. Applicant cites the office action of 9/24/07.

While the Office action may state that Applicant was in possession of a particular GAD65 peptide, it does not state that Applicant was in possession of the claimed method of administering an Ig-GAD65 peptide construct as claimed.

Regarding A) Applicant cites pages 45, 46, 19, 22, 23, and 24 of the specification in support.

A review of pages 45 and 46, at the beginning of the Examples section, show that the peptide of SEQ ID NO:4 is disclosed just once, and only in the context of a peptide. It is not disclosed in the context of the claimed method of administering an Ig-GAD65 peptide construct. Indeed, the disclosure of the examples is limited to the production and administration of a single Ig-insulin peptide (Ig-INS β) and an Ig-hen egg lysozyme (Ig-HEL) control peptide. Regarding the disclosure at page 19, GAD2 is disclosed. Regarding the disclosure at pages 22-24, "Ig-GAD2" is disclosed. It is noted that nowhere in the specification is "Ig-GAD2" defined, accordingly it cannot provide a written description for the Ig construct employed in the method of the instant claims.

10. The following are new grounds for rejection.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically

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disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 2, 4, 5, 7, 13, 15-19, 22-24, 26, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 in view of Chao et al. (1999).

WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM, (see particularly pages 10 and 19) employing an engineered fusion protein, e.g., a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop (see particularly Figure 1, page 13, and Example II).

The method differs from the claimed invention only in that it does not teach the use of the GAD65 SEQ ID NO:4 peptide as the autoantigen employed for the treatment of IDDM.

Chao et al. teach that the GAD65 peptide of SEQ ID NO:4 (p206-220) is an immunodominant T cell diabetes antigen in their NOD mouse diabetes model (see particularly page 9300, Results).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of WO 98/30706 for the treatment of IDDM in a subject such as a mouse model of diabetes employing the p206-220 T cell autoantigen of Chao et al. One of ordinary skill in the art at the time the invention was made would have had reason to select the GAD65 p206-220 peptide as the autoantigen of choice for use in the claimed method because Chao et al. teaches that it was the most immunodominant diabetes T cell antigen in their model. Regarding the timing of administration of the Ig-fusion protein set forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention.

Applicant's arguments, filed 9/15/10, have been fully considered but are not found persuasive. Applicant argues that any obviousness rejection that relies on an alleged teaching, suggestion or motivation *must* be articulated in a *Graham v. Deere* format.

Applicant is simply in error, the *Graham v. Deere* format is just one of many that may be used in a finding of obviousness. It is the substance of a rejection, not the format that is critical.

Applicant alleges that the claims have been misinterpreted and that there would have been no expectation of success.

These argument have been addressed by the use of Chao et al. showing that the specific peptide of SEQ ID NO:4 was known at the time of the invention as an immunodominant T cell diabetes epitope.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla, can be reached on (571) 272-0735.

15. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

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